BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Attorney Docket No. DVME-1014USCON1
BOUCHER, CHARLES	:	
Serial No. 10/058,622	:	Group Art Unit: 1631
Filed: January 28, 2002	:	Examiner: CHANNING MAHATAN

For: METHOD FOR EFFECTING COMPUTER IMPLEMENTED DECISION-SUPPORT IN THE SELECTION OF THE DRUG THERAPY OF PATIENTS HAVING A VIRAL DISEASE

DECLARATION OF ANDREA DE LUCA PURSUANT TO 37 C.F.R. §1.132

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Andrea De Luca, hereby declare as follows:

2. My detailed *curriculum vitae* is attached hereto as Exhibit A.

3. I have reviewed the specification, drawings and currently pending claims of U.S. patent application no. 10/058,622. I have also reviewed the Office Action mailed on July 29, 2003 (hereinafter "the Office Action"), the applicant's response to the Office Action, which arrived at the United States Patent and Trademark Office (hereinafter "USPTO") on November 28, 2003, the Final Rejection mailed on February 24, 2004 (hereinafter "the Final Rejection"), the applicant's response to the Final Rejection, which arrived at the USPTO on April 26, 2004, and the Advisory Action mailed on May 12, 2004 (hereinafter "the Advisory Action").

4. I am informed that claims 21-63 of the present application stand rejected under 35 U.S.C. §112, 1st paragraph, as failing to comply with the enablement requirement.

5. I am informed that the standard for determining whether the specification meets the

enablement requirement was set forth in *Mineral Separation v. Hyde*, 242 U.S.261,270 (1916), which posed the question, "is the experimentation needed to practice the invention undue or unreasonable?"

6. I am also informed that the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731,737,8 USPQ2d 1400, 1404 (Fed.Cir.1988) and MPEP §2164.01(a).

Claim 21

7. With regard to the breadth of claim 21, claim 21 of the present application is relatively narrow since it requires the use of a rules database wherein each rule indicates the suitability of a drug for treatment of a specific viral genotype. Moreover, the method of claim 21 displays drugs suitable for therapy in a ranking based on their suitability indication. The suitability indication is based on at least a combination of: (a) a first value indicating resistance level of the genotype for that drug, and (b) a second value indicating the confidence in the first value. Thus, to perform the method of independent claim 21, a skilled person must be able to provide a rules database that gives a suitability indication, based on the first and second values (a)-(b).

8. With regard to the nature of the invention, the invention relates to a method for computer implemented decision support in selection of drug therapy. As such, the invention lies in an improved computer implementation of a specific type of mental process that doctors carry out on a regular basis, albeit without computer implementation. More particularly, doctors currently make selections of appropriate drug therapies. Such selections are often based on factors such as the resistance level of a particular genotype for a particular drug, as well as the degree of confidence the doctor has in the information that is relied upon for determining the resistance level of that genotype for that drug. Therefore, the nature of the invention is such that the skilled person already knows how to select a drug therapy, by the performance of a mental process, using the type of information required by claim 1 of the present application.

9. The state of the prior art is evidenced by, for example, two of the documents of record in the present application, namely, "CTSHIV: A Knowledge-Based System for the Management of HIV-infected Patients," Pazzani et al., *Proceedings: Intelligent Information Systems, IIS' 97* (CAT. No. 97TB100201), 1997, pages 7-13 (hereinafter "Pazzani et al."); and "Knowledge-Based Avoidance of Drug-Resistant HIV Mutants," Lathrop et al., *American Association of Artificial Intelligence*, 1998, pages 1071-1078 (hereinafter "Lathrop '98"). Lathrop '98 describes the CTSHIV system that is employed in the method of Pazzani et al.

10. The level of ordinary skill in the art is high. Specifically, Lathrop'98 describes an AI system (CTSHIV) that connects the scientific literature describing specific HIV drug resistances directly to the customised treatment strategy of a specific HIV patient. Rules in the CTSHIV knowledge base encode knowledge about sequence mutations in the HIV genome that have been found to result in drug resistance to the HIV virus. The rules represent knowledge about HIV drug resistance as a set of if-then rules of the form:

IF <antecedent> THEN <consequent> [weight]

The system described in Pazzani et al. uses the CTSHIV expert system that is described in Lathrop '98. Thus, from Pazzani et al. and Lathrop '98, it is clear that the skilled person already knows how to implement a rules database wherein a suitability indication is based on a value indicating resistance level of the genotype for that drug, i.e. element (a) of claim 1 of the present application.

11. Lathrop '98 also teaches that, "The weight associated with a rule is not a confidence as in many expert systems. Rather it reflects the estimated level of resistance to a particular drug." (See page 1073, last paragraph of Lathrop '98). This statement indicates that, as of 1998, there were many expert systems in existence, which employed a confidence value to determine the weight associated with a particular rule in a knowledge-based system. In my opinion, this demonstrates that, as of 1998, a skilled person was capable of implementing element (b) of claim 1 of the present application, namely, basing a suitability indication on a value indicating the confidence in the value indicating a resistance level of the genotype for that drug.

12. The level of predictability in the art of computer-implemented decision support is very high since this art involves the application of a rules database, using a computer. Thus, a skilled person can predict, from knowledge of the rules database, what the outcome of the method will be. The skilled person can also predict the effect of a change in the rules database on the outcome of the method, from knowledge of the rules database.

13. A very significant amount of direction is provided in the present application for implementation of the method of claim 1. For example, the specification discusses how the conferred resistance by substitution is derived and how a value is assigned indicative of resistance level. See page 3, line 31, to page 5, line 11, of the application as originally filed. This part of the application explains, among other things, that the information on the conferred resistance by substitutions is obtained from scientific articles and evaluations by pharmaceutical companies, which information is carefully

examined by the experts of a core-committee. In the end the core-committee assigns a value indicating the resistance level. See page 4, lines 15-18 of the application as originally filed. In my opinion, the direction given in the application on how to assign a value indicating the resistance level, is sufficient for a person skilled in the art to implement this aspect of the claimed invention since, as discussed above with respect to the state of the art, the skilled person already knows, from Pazzani et al. and Lathrop '98, how to create a rules database which assigns a value indicating resistance level.

14. Also, the specification at page 5, line 35, to page 6, line 6, sets forth an example of how to determine the confidence level. In this example, objective criteria are employed. Specifically, the confidence level may be one of three levels, namely, (1) the drug result is based on suggestive evidence, (2) the drug result is proven *in vitro*, or (3) the drug result is proven *in vivo*. In my opinion, it is straightforward for a person of ordinary skill in the art to assign a confidence level on this basis since that person need only read the experimental portion of the information in question to determine whether tests were carried out *in vivo*, *in vitro*, or otherwise. Moreover, the skilled person is already familiar with expert systems employing confidence levels as weighting factors, as discussed above with respect to Lathrop '98, and thus would have no difficulty in implementing the present method based on the application of common general knowledge and the detailed teaching of how to assign a confidence level that is provided in the present specification at page 5, line 35 to page 6, line 6.

15. In addition, the specification of the present application describes how to assign the suitability level at page 6, lines 8-26. This description is sufficient for a skilled person because the suitability level is the resistance level weighted based on a confidence value. As discussed above, Lathrop '98 makes it clear that many expert systems already existed as of 1998 wherein a first value is weighted based on a second confidence value.

16. Furthermore, the present specification extensively describes the manner of updating the rules database on page 3, line 31, to page 4, line 18, of the application as originally filed. Specifically, the rules database is updated by a core committee that periodically

reviews, on a frequent basis, the latest publications on the subject and decides which adjustments should be made to the rules, based on these latest publications.

17. The present specification contains an extensive working example at pages 7-12 and in Figures 1-3 of the present specification.

18. In my opinion, essentially no experimentation is required to implement the present invention based on the disclosure of the application as filed, taken in combination with the common general knowledge of a skilled person. As discussed above, the skilled person already knows how to assign a first resistance value from Pazzani et al. and Lathrop '98, the specification provides an objective method of determining a confidence value that can easily be carried out by a skilled person, and the skilled person already knows how to weight a first value based on a confidence value, as can be concluded from Lathrop '98 which teaches that many such expert systems were already in existence in 1998.

Claim 44

19. The method of claim 44 can be carried out by a skilled person in the same manner as discussed above with respect to claim 21, except that in the method of claim 44, the rules database must include a rule for determining the suitability of a drug for treatment of a specific viral genotype, when that drug is taken in combination with another drug.

20. In my opinion, the skilled person can implement the method of claim 44 with essentially no experimentation since the skilled person can easily implement the only further step required by claim 44, that is not present in the method of claim 21. For example, the skilled person can formulate a rule for determining the suitability of a drug for treatment of a specific viral genotype, when that drug is taken in combination with another drug in the same manner that the first value indicating resistance level is formulated in the method of claim 21, except that in this case the skilled person would refer to information relating to particular combinations of drugs to formulate the resistance value, rather than to information relating to the use of individual drugs. Thus, the skilled person would have no difficulty in implementing the method of claim

44 of the present application in view of the disclosure of the present specification and the common general knowledge of a person skilled in the art.

Claim 51

21. The method of claim 51 can be carried out by a skilled person in the same manner as discussed above with respect to claim 21, except that in the method of claim 51, the rules database must include a rule for determining the suitability of a drug for treatment of a specific viral genotype which takes into account the level of the drug in a patient.

22. In my opinion, the skilled person can implement the method of claim 51 with essentially no experimentation by including as a data input to the rules database, the level of the drug in the patient, as specified in the information relied upon for creation of the rules database. Then, when a suitability indication is desired, the skilled person may specify or determine the desired drug level so that the rules database will limit its consideration of information to only information relevant to the specified drug level. This will generate a list of drug therapies, which are based on a resistance value at a particular drug level, as required by the method of claim 51.

Claim 60

23. The method of claim 60 can be carried out by a skilled person in the same manner as discussed above with respect to claim 21, except that in the method of claim 60, the rules database must include a rule for determining the suitability of a drug for treatment of a specific viral genotype which takes into account the clade of a virus.

24. In my opinion, the skilled person can implement the method of claim 60 with essentially no experimentation by including as a data input to the rules database, the clade of the virus, as specified in the information relied upon for creation of the rules database. Then, when a suitability indication is desired, the skilled person may specify or determine the clade so that the rules database will limit its consideration of information to only information relevant to the specified clade. This will generate a list of drug therapies, which are based on a resistance value for a particular virus clade, as required by the method of claim 60.

Dependent Claims

25. Some of the dependent claims of the present application require rules for different protein substitutions and/or type of drug activity. In my opinion, the skilled person can implement the methods of these dependent claims with essentially no experimentation by including as a data input to the rules database, the protein substitutions and/or type of drug activity, as specified in the information relied upon for creation of the rules database. Then, when a suitability indication is desired, the skilled person may specify the protein substitutions and/or type of drug activity so that the rules database will limit its consideration of information to only information relevant to the specified protein substitutions and/or type of drug activity. This will generate a list of drug therapies, which are based on a resistance value for a particular protein substitution and/or type of drug activity, as is required by these dependent claims.

26. Some of the dependent claims of the present application require consideration of clinical experience in determining a suitability indication. According to the specification at page 6, lines 27-31, clinical experience can mean experience provided by experts, or it can comprise the outcome of clinical studies relating the presence of substitutions at the start of therapy directly to clinical or virological outcome. In my opinion, substantially no experimentation is required to consider clinical evidence in determining a suitability indication. For example, in the case of experience provided by experts, the experts can simply weight the suitability indication based on their own clinical experience, e.g. an expert that has a significant amount of favorable clinical experience will raise the suitability indication to reflect the favorable clinical experience. In the case of using the outcome of clinical studies as the clinical experience, the incorporation of this information can be done in essentially the same way that the information relating to the resistance level is incorporated into the rules database.

27. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that the statements were made with the knowledge that willful false statements and the like

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

By: Andrea De Luca

Andrea De Luca

Dated: June 18, 2004

CURRICULUM VITAE

Andrea De Luca, M.D.

Istituto di Clinica delle Malattie Infettive,
Università Cattolica del Sacro Cuore
Policlinico Universitario "Agostino Gemelli"
Largo A Gemelli 8 –00168 Roma
Tel +39 06 3015 4945;
Fax +39 06 3054 519;
E: andrea.deluca@rm.unicatt.it

Born in Chieti (Italy) August 23, 1964
Graduated in Medicine in 1989, specialized in Infectious Diseases in 1993 and became Assistant Professor of Infectious Diseases in 1995 at the Catholic University of Sacred Heart, Rome, Italy.

Current position:

- Physician Director in Infectious Diseases at the University Polyclinic "Agostino Gemelli", Rome, Italy
- Member of the Scientific Committee, the Drug Resistance Committee and the Hepatitis Committee of the Italian Cohort I.Co.N.A of HIV-infected patients.
- Chair, member of the organising committee or of the programme committee of several European and International workshops and conferences on HIV

Dr De Luca has published about 100 scientific papers cited in PubMed with a sum of Impact Factor (ISI-SCI 2002) of 435. A list of relevant publications stating his position with respect to HIV drug resistance is enclosed.
He has made over 300 presentations at national and international conferences and is author of several chapters on Textbooks of Infectious Diseases.

The research activity of Dr De Luca has focused mainly on

- Clinical studies on the treatment of HIV infection (efficacy, toxicity, adherence)
- Genotypic and phenotypic HIV drug resistance, pharmacokinetics and pharmacogenomics of antiretrovirals

Dr De Luca has helped developing pilot programs for the introduction of antiretroviral treatment in Mozambique; he coordinates the clinical follow up of 1,300 HIV-infected patients in his clinic.

CURRICULUM VITAE

Relevant Publication list

Andrea De Luca, M.D.

De Luca A, Perno CF.
Impact of different HIV resistance interpretation by distinct systems on clinical utility of resistance testing. Curr Opin Infect Dis. **2003** Dec;16(6):573-80.

De Luca A, Antinori A, Di Giambenedetto S, Cingolani A, Colafigli M, Perno CF, Cauda R. *Interpretation systems for genotypic drug resistance of HIV-1.*Scand J Infect Dis Suppl. **2003** Dec;35 Suppl 106:29-34.

De Luca A, Cingolani A, Di Giambenedetto S, Trotta MP, Baldini F, Rizzo MG, Bertoli A, Liuzzi G, Narciso P, Murri R, Ammassari A, Perno CF, Antinori A.
Variable prediction of antiretroviral treatment outcome by different systems for interpreting genotypic human immunodeficiency virus type 1 drug resistance. J Infect Dis. **2003** Jun 15;187(12):1934-43.

Zaccarelli M, Perno CF, Forbici F, Cingolani A, Liuzzi G, Bertoli A, Trotta MP, Bellocchi MC, Di Giambenedetto S, Tozzi V, Gori C, D'Arrigo R, De Longis P, Noto P, Girardi E, **De Luca A**, Antinori A.
Using a database of HIV patients undergoing genotypic resistance test after HAART failure to understand the dynamics of M184V mutation. Antivir Ther. **2003** Feb;8(1):51-6.

Van Laethem K, **De Luca A**, Antinori A, Cingolani A, Perna CF, Vandamme AM.
A genotypic drug resistance interpretation algorithm that significantly predicts therapy response in HIV-1-infected patients. Antivir Ther. **2002** Jun;7(2):123-9.

Cingolani A, Antinori A, Rizzo MG, Murri R, Ammassari A, Baldini F, Di Giambenedetto S, Cauda R, **De Luca A**.
Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). AIDS. **2002** Feb 15;16(3):369-79